AMENDMENTS TO THE SPECIFICATION

Page 1, under the title, please insert the following:

CROSS REFERENCE TO RELATED APPLICATIONS

This application is a 35 U.S.C. §371 National Stage filing of International Application PCT/GB98/02115, filed July 16, 1998, which claims priority to Great Britain application no. 9714971.0, filed July 16, 1997.

Page 18, line 36 to page 19, line 18, replace with the following rewritten paragraph:

Figure 5: ATM phosphorylated p53 at Ser15 and Thr18 in the presence of DNA. Kinase reactions employing ATM and p53 were performed in the presence and absence of DNA. These studies revealed phosphorylation of p53 was increased in the presence of DNA. (A/B) Bands corresponding to ^{32}P-labelled p53 were excised from a gel, digested with trypsin, and chromatographed on a Vydac 218TP54 C18 column (see experimental procedures). Purified p53 fractions phosphorylated by ATM preparations in the presence, but not in the absence, of DNA (peptides 2a, 2b and 2c) were subjected to peptide sequence analysis as described in Experimental Procedures; radioactivity was measured after each cycle of Edman degradation. The putative amino acid sequence of the p53 peptide showing incorporation of ^{32}P is indicated in panel C (SEQ ID NO:26). (D) Tryptic peptide map of p53 phosphorylated by DNA-PK in the presence of DNA. Kinase reactions containing DNA-PK and p53 were performed in the presence of linear DNA and ^{32}P-labelled p53 was analysed as in (A,B), again revealing phosphorylation at Ser15 and Thr18.

Page 19, lines 20-35, replace with the following rewritten paragraphs:

Figure 6a shows the amino acid sequence of human ATM (SEQ ID NO:1), with the kinase domain marked by underlining. Figures 6b ii - vii ~~shows~~ show the ATM nucleic acid sequence (SEQ ID NO:2) with the initiation codon underlined.

Figure 7a shows the amino acid sequence of human p53 (SEQ ID NO:3) with residues phosphorylated by ATM marked by underlining. Figures 7b I-ii ~~shows~~ show the p53 nucleic acid sequence (SEQ ID NO:4) with the initiation codon underlined.

Figure 8a shows the amino acid sequence of human ATR (FRP-1) (SEQ ID NO:5). Figures 8b I – vi ~~shows~~ show the ATR nucleic acid sequence (SEQ ID NO:6) with the initiation codon underlined.

Figures 9a I - ii ~~shows~~ show the amino acid sequence of DNA-PKcs (SEQ ID NO:7). Figures 9b I – ix ~~shows~~ show the DNA-PK nucleic acid sequence (SEQ ID NO:8) with the initiation codon underlined.

Page 24, lines 6-19, please replace with the following rewritten paragraph:

Preferably the amino acid sequence shares homology with a fragment of the relevant ATM or p53 fragment sequence shown preferably at least about 30%, or 40%, or 50%, or 60%, or 70%, or 75%, or 80%, 90%, or 95% homology. Thus, a peptide fragment of ATM or p53 may include 1, 2, 3, 4, 5, greater than 5, or greater than 10 amino acid alterations such as substitutions with respect to the wild-type sequence. Preferably the peptide fragments of ATM are based on the sequence of all or part of the kinase domain as shown in Figure 6. Preferably, the p53 fragments are based on the N-terminal sequence of the molecule around the sites phosphorylated by ATM, i.e. comprising the amino acid motif (SEQ ID NO:9) PPLSQETFSD, or more generally, the motif (SEQ ID NO:10) SxxT, where x is any amino acid.

Page 55, lines 1-8, replace with the following rewritten paragraph:

A polypeptide, peptide or other substance able to modulate able to ~~modlate~~ modulate or interfere with the interaction of the relevant polypeptide, peptide or other substance as disclosed herein, or a nucleic acid molecule encoding a peptidyl such molecule, may be provided in a kit, e.g. sealed in a suitable container which protects its contents from the external environment. Such a kit may include instructions for use.

Page 68, lines 6-27, replace with the following rewritten paragraph:

Effect of p53 phosphorylation on interaction with Mdm2

To test whether phosphorylation on Ser15 or Thr18 of p53 affects its interaction with Mdm-2, phosphorylated and unphosphorylated p53-derived peptides were generated and were assessed for Mdm-2 binding by ELISA analysis. The four peptides used contained p53 residues 11 to 25 (in the sequence (SEQ ID NO:11) NH2-SGSGEPPLSQETFSDLWKL-COOH; where the underlined sequence is that derived from p53) that were unphosphorylated (1); phosphorylated on residue equivalent to p53 residue Ser15(2); phosphorylated on residue equivalent to p53 residue Thr18(3); or phosphorylated on two residues, equivalent to p53 residue Ser15 and Thr18(4). Binding of Mdm-2 derivatives occurred effectively with unphosphorylated peptide 1 but was found to be inhibited dramatically in the cases of peptides 3 and 4, which contained phosphorylated Thr18. In contrast, binding was only impaired slightly by phosphorylation on Ser15 (peptide 2). We therefore conclude that phosphorylation on Thr18

of p53 has a dramatic effect on its interaction with Mdm-1 and that phosphorylation of this site is likely to play a key role in regulating p53 responses *in vivo*.

Page 75, lines 33-37, replace with the following rewritten paragraph:

ds 15-mer (SEQ ID NO:12) 5' B-CCTGCCCTTGCCTGA-3'

(SEQ ID NO:13) 5' TCAGGCAAGGGCAGG-3'

ds 25-mer (SEQ ID NO:14) 5' B-CCTGCCCTTGCCTGACGCTATTAGT-3'

(SEQ ID NO:15) 5' ACTAATAGCGTCAGGCAAGGGCAGG-3'

Page 76, lines 1-37, replace with the following rewritten paragraph:

(SEQ ID NO:16) 5' B-TTGTAAAACGACGGCCAGTGAATTCATCATCAATAATATACC TTATTTTG-3'

(SEQ ID NO:17) 5'CAAAATAAGGTATATTATTGATGATGAATTCACTGGCCGTCGTTTTACAA-3'

ds75-mer

(SEQ ID NO:18)5' B-GATCGAATCCGATAGAGTATAGATAGAGTAAAGTTTAAATACTTA TATAGATAGAGTATAGATAGAGGGTTCAAA-3'

(SEQ ID NO:19) 5'TTTGAACCCTCTATCTATACTCTATCTATATAAGTATTTAAAC TTTACTCTATCTATACTCTATCGGATTCGATC-3'

ss 50-mer

(SEQ ID NO:20) 5' B-TTGTAAAACGACGGCCAGTGAATTCATCATCAATAATATACCTT ATTTTG 3'

For the following, a biotinylated 100-mer oligonucleotide (DYNO) was used as a "backbone" to which other oligonucleotides were annealed.

(SEQ ID NO:21) DYNO 5' B-CCTGCCCTTGCCTGACGCTATTAGTTCATCTATTTGTTTTG CTAATTCGATTGGAATCGAAACGGTCACATATTCTTTTTTGACTGATTTCCTCGGCATA-3'

nicked oligo, DYNO + DAM2 + DAM3:ds/ss transition, DYNO + DAM3; gapped ds oligo, DYNO + DAM3 + DAM5; 10 bp insertion, DYNO + DAM6.

DAM2:

(SEQ ID NO:22) 5'TATGCCGAGGAAATCAGTCAAAAAAGAATATGTGACCGTTTCGATTCCAA-3'

DAM3:

(SEQ ID NO:23) 5'TCGAATTAGCAAAACAAATAGATGAACTAATAGCGTCAGGCAAGGGCAGG-3'

DAM5: (SEQ ID NO:24) 5' TATGCCGAGGAAATC-3'

DAM6: (SEQ ID NO:25)

5' TATGCCGAGGAAATCAGTCAAAAAAGAATATGTGACCGTTTCGAATTAGCAAAACAAATAGATGA ACTAATAGCGTCAGGCAAGGGCAGG-3'